Body mass index (BMI): association with clinicopathological factors and outcome of women with newly diagnosed breast cancer in New Zealand

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ABSTRACT

AIMS: To identify associations of obesity with breast cancer and its outcome in a New Zealand population, including those treated with adjuvant chemotherapy.

METHODS: Data was collated from four regional Breast Cancer Registers, Auckland, Waikato, Wellington and Christchurch, for all women with newly diagnosed breast cancer, with weight and height recorded. Associations of body mass index (BMI) with patient and tumour characteristics, and all-cause mortality were determined.

RESULTS: BMI was available for 5,458 new breast cancers, 27% of all registered. BMI was normal (18.5–24.9kg/m^2) for 32.7%, overweight (25–29.9kg/m^2) 31.1%, obese (>30kg/m^2) 34.9% and 1.3% underweight (<18.5kg/m^2). Median age was 55 years. Higher BMI was associated with non-European ethnicity, post-menopausal status, screen-detection, older age and tumours with higher grade, greater size and positive progesterone receptors. Mean survival for women younger than 56 years was 18.0 years for normal BMI and 14.8 years for BMI >35 (p=0.055, Log-rank). Women younger than 56 years treated with adjuvant chemotherapy had lower survival if obese compared with normal BMI (p=0.055, Log-rank).

CONCLUSIONS: High BMI was associated with larger tumours, of higher grade, progesterone receptor positive and post-menopausal status. Obese pre-menopausal women treated with adjuvant chemotherapy had a trend to poorer outcome.

Obesity is increasing in the New Zealand population, with nearly two-thirds of New Zealand women overweight or obese.[1] Evidence is strengthening that obesity is not only associated with increased risk of developing breast cancer, but also with a poorer outcome once diagnosed.[2,3] Reports of poorer outcomes in obese women are inconsistent, and some suggest an association with menopausal status and breast cancer subtype.[4,5] Review of the International Breast Cancer Study Group adjuvant chemotherapy trials shows a poorer outcome for pre- or peri-menopausal obese women.[6]

Explanations proposed for the poor outcome associated with obesity have included inadequate dosing of chemotherapy, effects of the metabolic syndrome and inflammation associated with adipose tissue.[7] In addition, both exercise and weight loss reduce estrogen levels.[8,9] Thus, reduction of obesity and exercise are promoted as ways to improve breast cancer outcome, with their relative contributions yet to be clarified.[10] Our laboratory studies have shown that cancer-associated adipocytes, known as CAAs,[11] co-cultured with triple negative or estrogen receptor-positive breast cancer cell lines protect the cancer

cells from two common chemotherapy drugs used for breast cancer (Phillips, Currie, unpublished). Metformin (a drug widely used to treat obesity-related type 2 diabetes) prevented this chemotherapy resistance at clinically relevant concentrations.

The overall aim of our study was to understand the prevalence of obesity in New Zealand women with breast cancer, and to discover any associations with clinical or tumour characteristics, and whether there was any impact on outcome in a population-based patient group. Specifically, we also determined the effect of obesity on outcomes after adjuvant chemotherapy. The study used the four Breast Cancer Registers in New Zealand, which record all new breast cancers diagnosed in their region, an estimated 55% of national diagnoses in 2013.[12]

Methods

Patients

The four regional Breast Cancer Registers in New Zealand were searched for women who had body weight and height recorded at the time of their first diagnosis of a breast cancer, enabling calculation of body mass index (BMI). The register in Auckland has been entering patients for 15 years, Waikato 10 years, Christchurch six years and Wellington five years. Eligible patients were those recorded in the registers with a tissue diagnosis date for their first breast cancer prior to 31 December 2014, to enable at least one year follow-up. Recording of height and weight has been more frequent in the last five years. Where menopausal status was not known, women older than 55 years at diagnosis were recorded in the registers as post-menopausal.

Treatment

Women were managed in their regional centre, according to nationally accepted guidelines, with routine imaging by bilateral mammography, ultrasound if needed, and magnetic resonance imaging (MRI) of the breasts when indicated. Over the study period, sentinel node biopsy gradually became the standard for T1 (less than 2cm) and small T2 tumours, with earlier patients having level 1 and 2 axillary dissection. Patients with risk factors for local recurrence after mastectomy and those having breast conservation were referred to the regional radiation oncology service, and those with risk factors for distant spread were referred to the regional medical oncology service to consider systemic adjuvant therapies. Patients with locally advanced disease received neoadjuvant systemic therapy, prior to surgery and radiation. Standard adjuvant chemotherapy regimens were based on anthracyclines and taxanes, following international guidelines. Women with human epidermal growth factor receptor-2 (HER2) positive tumours received trastuzumab with chemotherapy when chemotherapy was indicated. Women with estrogen receptor (ER) positive tumours were offered adjuvant endocrine therapy, following international guidelines. Reconstructive surgery was performed either at the initial operation or some years later. Women with more than four nodes involved, locally advanced primary tumours, or suspicious symptoms or signs underwent staging with blood tests (blood count, liver and renal function, including calcium), computerised tomography (CT) scan of chest, abdomen, pelvis and bone scan. Other imaging was undertaken when indicated clinically. Positron emission tomography-computerised tomography (PET-CT) scan imaging using fluoro-deoxy glucose (FDG) or sodium fluoride (NaF) is not yet funded in the New Zealand public health service so was rarely used. In all centres regular multidisciplinary meetings review staging and pathology, and make management decisions.

Statistics

The demographic details, age, breast cancer type and stage, estrogen, progesterone and HER2 receptor status, treatment and outcome were collated from the registers. The WHO definitions[13] were used to group BMI, with normal BMI defined as 18.5–24.9kg/m^2, overweight 25–29.9kg/m^2, with obese level 1 defined as 30–34.9kg/m^2, obese level 2 as 35–39.9kg/m^2, obese level 3 as >39.9kg/m^2, and underweight as <18.5kg/m^2. Ethnicity was self-reported and followed the New Zealand census definition. Post-menopausal status was taken as aged older than 55 years when not known. The associations between patient and tumour factors and BMI group were determined using Pearson's correlation coefficients and one-way ANOVA as appropriate. Factors showing significant univariate associations with BMI were then entered into a general linear model with BMI as the dependent variable to determine the significant independent associations with BMI. All-cause

mortality was determined for the entire group of women. After excluding patients with more than one breast cancer, and those with metastases at presentation, the associations between BMI, age group, menopausal status, nodal status, tumour T stage, receptor status and chemotherapy usage and all-cause mortality were analysed using Log-rank tests and Cox proportional hazards regression models, and using Kaplan Meier curves. The outcome for women who received adjuvant chemotherapy was explored by BMI and menopausal status.

Ethics

The registers themselves are approved by the regional Health and Disability Committees, including approval from their regional Health and Disability Ethics Committee to release de-identified data of patients on the registry databases, and this study was approved by the University of Otago Ethics Committee (12/319).

Results

Clinicopathological factors

There were 5,458 new breast cancers diagnosed in women with BMI recorded from the four regional registers (comprising 27% of the total 20,056 registrations in the four registers), 1,261 from Auckland (10% of registrations), 4,787 from Waikato (57% of registrations), 464 from Wellington (32% of registrations), 1,009 from Christchurch (55% of registrations). The Auckland register has operated for the longest period of time, and had the lowest proportion of women with height and weight recorded. The patient demographic and clinicopathological data at diagnosis for these 5,458 tumours are shown in Table 1. Approximately one-third were of normal BMI (18.5–24.9kg/m^2), one third overweight (25.0–29.9kg/m^2) and one-third obese (BMI>30kg/m^2). The median age was 55 years. The majority (77.4%) were New Zealand European ethnicity, 13.4% New Zealand Māori, 5.2% Asian, 3.4% Pacific Island and 0.6% other.

Table 1: Clinicopathological characteristics at diagnosis for all breast cancers in women who had BMI recorded at diagnosis (number of cancers=5,458).

Characteristic	Subgroup	Number	Percent of total
Total		5,458	100
BMI, kg/m2	<18.5 underweight	73	1.3
	18.5–24.9 normal	1,785	32.7
	25–29.0 overweight	1,697	31.1
	30–34.9 obese 1	1,074	19.7
	35–39.9 obese 2	487	8.9
	40 + obese 3	342	6.3
Ethnicity	European	4,217	77.5
	Māori	727	13.4
	Asian	281	5.2
	Pacific	185	3.4
	Unknown	33	0.6
Presentation of cancer	Screening	1,881	34.5
	Symptomatic	3,558	65.2
	Unknown	19	0.3
Age at diagnosis	<40 years	486	8.9
	40–49 years	1,402	25.7

Table 1: Clinicopathological characteristics at diagnosis for all breast cancers in women who had BMI recorded at diagnosis (number of cancers=5,458) (Continued).

	50–59 years	1,546	28.4
	60–69 years	1,154	21.1
	70–79 years	574	10.5
	>79 years	294	5.4
Menopausal status	Post-menopausal	3,102	56.7
	Pre/peri-menopausal	2,356	43.1
Tumour histology	Ductal	4,432	81.2
	Lobular	564	10.3
	Other, unknown	462	8.5
Tumour grade	Low	834	15.3
	Intermediate	2,424	44.4
	High	1,959	35.9
	Unknown	241	4.4
Tumour stage	T1 (<20mm)	2,490	45.6
	T2 (20–49mm)	2,232	40.8
	T3, T4 (>49mm, locally advanced)	690	12.5
	Unknown	46	0.1
Tumour estrogen receptor	Positive	4,163	76.3
	Negative	1,189	21.8
	Unknown	106	1.9
Tumour progesterone receptor	Positive	3,392	62.1
	Negative	1,919	35.2
	Unknown	147	2.7
Tumour HER2 status	Positive	1,038	19.0
	Negative	3,397	62.2
	Unknown	1,023	18.8
Tumour triple negative		548	10.0
Nodal status, axilla	Positive	2,496	45.8
	Negative	2,621	48.0
	Unknown	341	6.2
Vascular/lymphatic invasion	Present	1,633	29.9
	Absent	3,765	69.0
	Unknown	60	1.1
Metastases at diagnosis	Present	285	5.2
	Not detected	1,801	33.0
	Staging not indicated	3,372	61.8
	Unknown	16	0.2

Table 2: Associations of BMI with patient demographic factors and tumour characteristics, univariate analyses. P-values are derived from Pearson's correlation coefficients and ANOVA.

Characteristic	Number in analysis	P value
Ethnicity	5,443	**<0.001**
Age at diagnosis	5,458	**0.015**
Menopausal status	5,458	**0.024**
Screening vs symptomatic	5,439	**<0.001**
Histology type	5,427	0.815
Tumour size	5,192	**<0.001**
Tumour grade	5,217	0.035
Estrogen receptor	5,352	0.365
Progesterone receptor	5,311	**<0.001**
HER2 status	4,435	0.26
Number positive nodes	5,117	0.133
Distant metastases	2,086	0.195

Associations with high BMI

Univariate analysis (Table 2) showed that higher BMI was significantly associated with non-European ethnicity, post-menopausal status, detection by screening rather than presenting with symptoms, increasing age at diagnosis, as well as positive progesterone receptor on the tumour, higher grade and larger tumour size (p values less than 0.05 were regarded significant). On multivariate analysis, all these factors remained independently associated with BMI in the general linear model with the exception of age (data not shown).

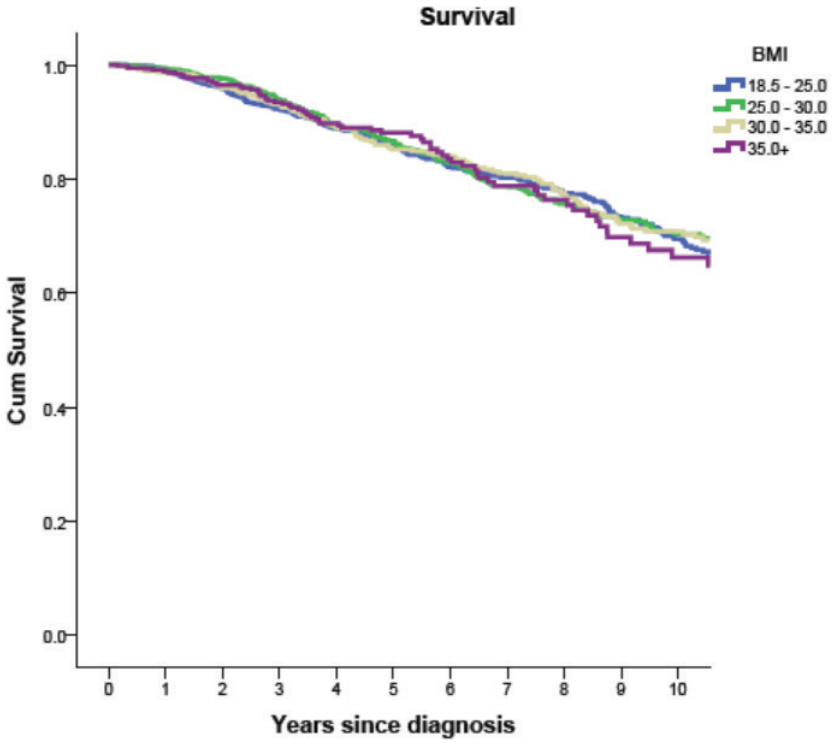
Outcome by BMI

All-cause mortality was analysed as the primary endpoint by Kaplan Meier method for the 5,150 women with a single primary cancer, by BMI group. Women with more than one primary cancer were excluded since survival could relate to either cancer. The normal, overweight and obese BMI groups each had a similar mean overall survival, 16 years, with median follow-up 3.2 years. Median survival was not reached. The underweight BMI group had a significantly poorer survival, with median and mean both eight years. The underweight women made up 1.3% of the whole group, and included 12.0% with metastatic disease, compared with 5.1% for normal or high BMI. Women with BMI less than the lower limit of normal were excluded from subsequent survival analyses, since low weight is associated with poorer outcome[2,14] due to inclusion of more women with metastatic disease or comorbidities. The Kaplan Meier survival curves by BMI, once women with metastases and BMI less than 18.5kg/m^2 were excluded, showed no distinguishable effect of raised BMI, with median follow-up of 3.2 years (Figure 1).

Age and menopausal status

The possible effect of age on impact of BMI on survival was explored, initially using all women with a single primary tumour, and excluding those with lower than normal BMI, shown in Figure 2. The cut-off using age 55 years or less, or older than 55 years was selected since 55 years was the median age, and also served as a surrogate for menopause. For women of 55 years of age or younger, mean survival was 17.0 years and decreased with higher BMI (18.0 years for normal BMI, 16.1 years for BMI 25–29.9kg/m^2, 16.3 years for BMI 30–34.9kg/m^2, and 14.8 years for BMI greater than 35kg/m^2, Log rank-test p=0.055; p<0.05 for significance). The women older than 55 years had mean survival of 13.7 years, and

Figure 1: Cumulative Survival (all-cause mortality), according to BMI as kg/m^2, for all women with a single primary breast cancer, after excluding those with metastases and those with BMI less than 18.5kg/m^2. Number of women is 1,601 for BMI 18.5–224.9kg/m^2, 1,538 for 25.0–29.9kg/m^2, 962 for 30.0–34.9kg/m^2, and 721 for >34.9kg/m^2.



this trended towards being longer at higher BMI (p=0.065, Log-rank test). For these older women, the mean all cause survivals were 12.3 years for normal BMI, 13.3 years for 25–29.9kg/m^2, 14.9 years for 30–34.9kg/m^2 and 14.2 years for BMI greater than 35kg/m^2. Thus, increased BMI had a non-significant adverse effect for younger women, and was potentially favourable for older women. The hazard rate for survival for women with BMI greater than 35kg/m^2 was significantly more favourable for those aged over 55 years (HR=0.72) compared with those aged less than 56 years (HR=1.40). Overall however, the effect of BMI on survival outcome and age did not reach significance (p=0.075).

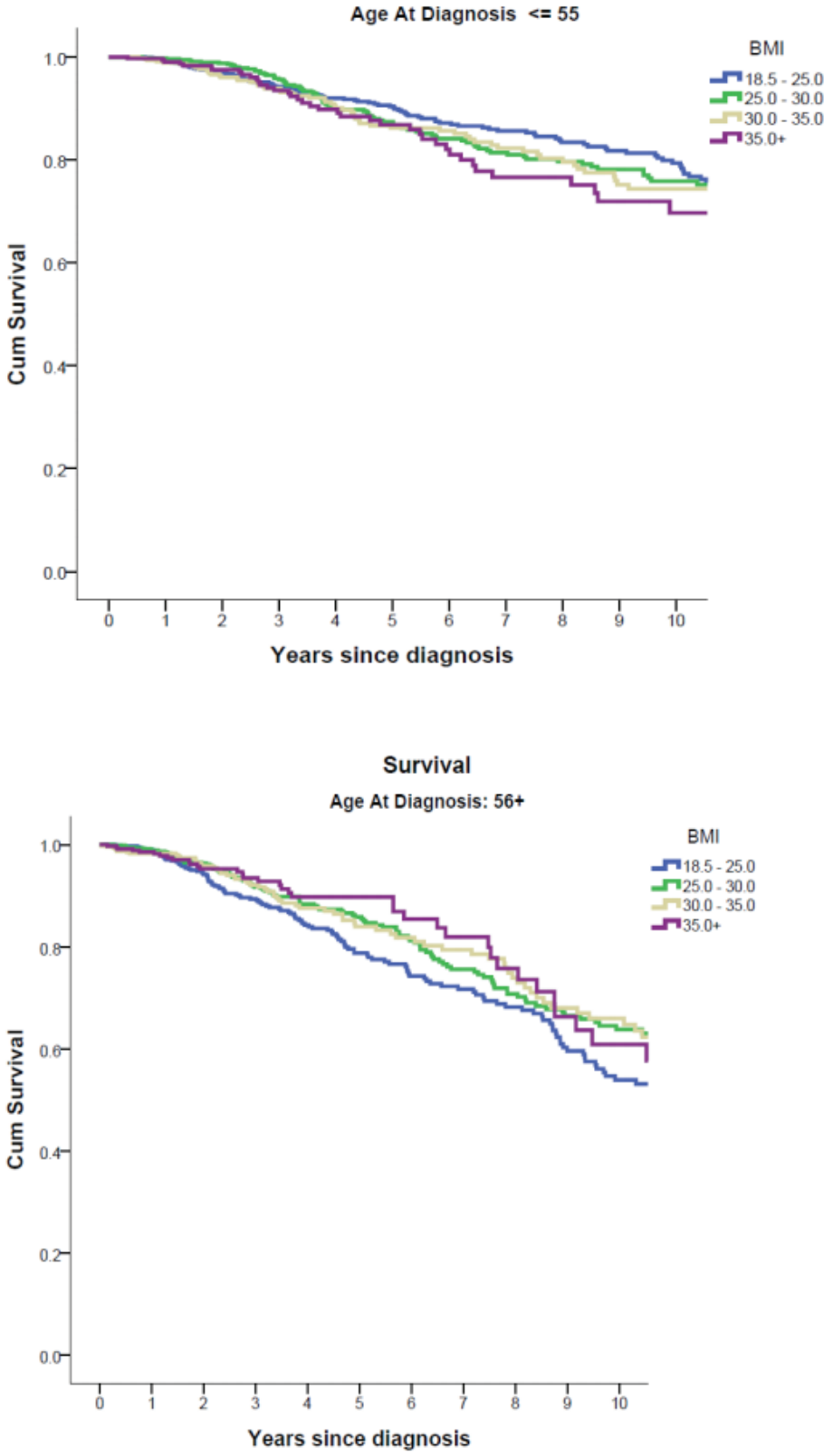
Pathological prognostic factors

Tumour and nodal features, which impact on outcome, were further explored with respect to interaction with BMI. Outcome by nodal status, for all ages, by BMI was determined, with mean survival 17.1 years for women with node-negative cancers (n=2,401), and 14.5 years for node-positive cancers (n=2,247). As expected, the effect of nodal status on survival was highly significant (HR=1.40, p<0.001). There were no significant effects on survival by BMI group according to nodal status, but the group with BMI greater than 35kg/m^2 tended to do better than normal weight if node-negative, and were trending to worse outcome than normal weight after five years when node-positive (data not shown). Tumour size or T stage had the expected effect on survival overall, but there was no effect by BMI group (data not shown). The expected higher prevalence of ER positive tumours at older age was seen, with 81.1% for age greater than 55 years, and 77.3% for younger women, but there was no significant variation in ER positivity by BMI and age greater than or less than 55 years, either for the whole group or just those receiving adjuvant chemotherapy.

Adjuvant chemotherapy

The number of women receiving adjuvant chemotherapy according to BMI status was explored. The women with metastatic disease at diagnosis were excluded along with those with more than one primary cancer, leaving 4,888 women with early disease for whom chemotherapy would be considered. The use of chemotherapy was similar for the normal (57.5% of women),

Figure 2: Cumulative Survival (all-cause mortality) for normal, overweight and obese BMI groups, according to age, greater or less than 55 years.



Includes 2,583 women 55 years of age or younger (top figure), and 2,239 older than 55 years (bottom figure), all with one breast cancer; excludes the lowest BMI group (less than 18.5kg/m^2).
For 55 years and younger, number of women is 922 for BMI 18.5–24.9kg/m^2, 809 for BMI 25.0–29.9kg/m^2, 491 for BMI 30.0–34.9kg/m^2, and 361 for BMI >34.9kg/m^2. For older than 55 years, number of women is 679 for BMI 18.5–24.9kg/m^2, 729 for BMI 25.0–29.9kg/m^2, 471 for BMI 30.0–34.9kg/m^2 and 360 for BMI >34.9kg/m^2.

overweight (58.1%) and high BMI groups (59.8% for BMI 30–34.9kg/m^2, 55.1% for BMI 35–39.9kg/m^2, and 55.3% for BMI of 40kg/m^2 and higher). However, a smaller percentage (38%) of underweight women (BMI <18.5kg/m^2) received chemotherapy. Since the effect of BMI on outcome may depend on menopausal status, or age greater or less than 55 years, and benefit of adjuvant chemotherapy declines with advancing age, survival (all-cause mortality) was examined for the women who were treated with chemotherapy, for those aged 55 years or younger, and those aged over 55 years, according to BMI. The BMI groups were defined for this analysis as normal and overweight combined (BMI=18.5–29.9kg/m^2), BMI 30–34.9kg/m^2, and BMI more than 35kg/m^2. The 1,964 women under 56 years on chemotherapy showed lower survival at high BMI (p=0.055, Log Rank), while the 826 women aged over 55 years showed no association of survival with BMI. For women who did not receive chemotherapy, 618 under 56 years and 1,413 over 55 years, there was no significant effect of BMI on all-cause mortality (data not shown).

To further explore the trend to poorer survival for more obese premenopausal women treated with chemotherapy, Kaplan Meier survival (all-cause mortality) was estimated for all premenopausal women, with one cancer and no metastases (n=2,231), by BMI group. The mean survival was 21.0 years overall, 21.7 years for BMI 18.5–24.9kg/m^2, 20.9 years for BMI 25–29.9kg/m^2, 20.2 years for BMI 30–34.9kg/m^2, 17.5 years for BMI 35–39.9kg/m^2 (p=0.045, compared with normal BMI, Log Rank (Mantel-Cox) by pairwise comparison) and 19.3 years for BMI of 40kg/m^2 or more (non-significant overall). Mean survival was determined for the cohort of premenopausal women with ER-positive tumours (n=1,704), and for the subset who had chemotherapy (n=1,181). Mean survival was 20.5 years and 20.4 years respectively, and there was no significant effect of BMI group (data not shown).

Discussion

Two-thirds of this large cohort of women with newly diagnosed breast cancers in four regions of New Zealand were overweight (31%) or obese (35 %). Higher BMI was significantly correlated with non-European ethnicity, post-menopausal status, detection by screening rather than presenting with symptoms, positive progesterone receptor on the tumour, increasing age at diagnosis and larger tumour size. Those women who had a BMI below normal (BMI<18.5kg/m^2) had significantly poorer outcome, while for women of normal, overweight or obese BMI, there was no effect of BMI on all-cause survival. Women with BMI greater than 35kg/m^2 had a proportionately poorer outcome if less than 56 years, compared with those older than 55 years. There was a poorer outcome for pre-menopausal women (less than 56 years of age) treated with adjuvant chemotherapy. Women with less than normal BMI were less likely to receive chemotherapy than normal weight women, while overweight and obese women had similar uptake rates to women of normal BMI.

The association of higher BMI with post-menopausal status, older age, detection by screening and larger primary tumour has been reported for other large population series.[2,3,6,15] The association with progesterone receptor status, separately from estrogen receptor status,[16,17] is hypothesised as due to its effect on peripheral aromatisation of estrogen.[15] While the larger primary tumour, detected by screening, might reflect more difficulty in detection in a larger breast, it could also reflect more aggressive biology, since higher grade is associated with obesity. The association of poorer outcome with increasing BMI in younger women, and with better outcome in older women, remain unexplained,[14,15] but supports the need for further studies into mechanisms such as estrogen metabolism, adipocyte effect on response of tumour cells to chemotherapy (Phillips, Currie, unpublished), insulin effects and inflammation.[7] The Breast Cancer Registers differ from the New Zealand Cancer Registry in each being dedicated to a specific region, and in recording much additional data, over and above the pathology, age and date of diagnosis. While they accrue all women diagnosed in the region, only women with height and weight recorded were included in this study, and their median age was five to ten years younger compared with national New Zealand Cancer Registry data

for the three years to 2013.[18] The distribution of BMI, however, closely matches that of the New Zealand female population.[1] The BMI group could be biased to women who needed their height and weight determined for receiving chemotherapy, or because of clinical concerns about their BMI. The clinicopathological data are similar to other patterns of care cohorts,[19] supported by the expected dependence of survival on axillary nodal positivity, tumour (T) stage and estrogen receptor status.

A poorer outcome on adjuvant chemotherapy has been reported on re-analysis of three large randomised clinical trials using anthracycline and taxanes (concurrent or sequential), with a poorer survival for BMI greater than 30kg/m^2 for the BIG-2-98 trial,[20] for BMI greater than 40kg/m^2 in the SUCCESS A trial,[21] and on long follow-up of ECOG E1199,[22] which also suggested a bigger effect for ER-positive tumours. Analysis of eight pooled trials of neoadjuvant chemotherapy showed a lower pathological complete response rate (pCR) to taxanes for high BMI.[23] A large meta-analysis[24] showed an adverse effect of increased BMI only in pre- or peri-menopausal women, and only for ER-positive tumours. In contrast, in the ADEBAR trial of sequential anthracycline and taxane, high BMI had an adverse effect on survival in post-menopausal women.[25] Our data, though only marginally significant, are consistent with an adverse effect of high BMI in younger women on chemotherapy, but analysis including only the ER-positive tumours did not reveal a stronger association of outcome with BMI. Strengths of this study are the relatively unselected inclusion of all women on the four registers, who had BMI determined, the overall large number of women for whom data had been collected prospectively, and that they received usual care, rather than having been eligible for a clinical trial with restrictive entry criteria. All-cause mortality is a sound end point, but may miss effects of BMI on breast cancer mortality alone. Analysis by receipt of adjuvant chemotherapy allowed a more homogeneous group to be studied to determine more clearly any effects of BMI on outcome after chemotherapy.

Weaknesses of the study are the younger age than the contemporaneous national registry data, the currently short median follow-up at 3.2 years and lack of disease-free survival endpoints, though these are less robustly recorded in observational studies than in randomised trials. The underweight women, who made up 1.3% of the BMI group, had a mean survival half that of the other women, as seen in other cohorts.[2,18] A higher proportion of the underweight women had metastases, and could have included women with comorbidity, which was not collected in the registers. There was no central review of pathology, although synoptic reporting was introduced during this period, and reporting became standardised between the registers. Drug doses and dose intensity have not been explored in this study, but will be the subject of a future study. Neutropenia has been reported to be more common at low or normal BMI than at high BMI,[26] suggesting relative underdosing at higher BMI and/or inappropriate dose reductions. Finally, appropriate BMI cut-offs for obesity may differ for different ethnic population groups,[1,13] and other measures such as waist circumference may better reflect risk.[13]

Implications and further research

This study shows that New Zealand women are likely to be similar to other women worldwide and that higher levels of obesity are likely to confer a poorer outcome for breast cancer, especially for younger women who receive adjuvant chemotherapy. Studies support greater benefit from combining weight loss with increased physical activity, but the specific requirements and mechanisms remain uncertain.[4,8,9] Both should be promoted to patients, and intervention studies continued, together with exploration of biomarkers, especially in obese women on adjuvant chemotherapy.

Conclusion

This study confirms the high frequency of high BMI, including severe obesity in women diagnosed with breast cancer, as in the female population of New Zealand. More obese women had larger primary tumours, were less likely to present with a symptomatic lump and more likely to have their breast cancer detected by screening, and tended to be older. The outcome for pre- and peri-menopausal women when treated with adjuvant chemotherapy as standard care tended to be poorer for those with very high BMI, offering preliminary results suggesting that real life outcomes are consistent with several recent publications from randomised clinical trials. Longer follow-up is needed together with ongoing research to uncover biomarkers for the adverse effects of high BMI, and to establish how weight loss and increased physical activity impacts on outcome. Clinicians need to record height and weight for all women with breast cancer.

Competing interests:
Dr Davey and Dr Robinson report grants from New Zealand Breast Cancer Foundation during the conduct of the study. Dr Morrin reports grants from New Zealand Breast Cancer Foundation and the Canterbury West Coast Division of the Cancer Society of New Zealand during the conduct of the study.

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REFERENCES:

1. Ministry of Health 2015a. Annual update of key results 2014/15: New Zealand Health Survey, 10 December 2015, on line publication, Wellington: Ministry of Health, New Zealand.
2. Chan D, Vieira A, Aune D, et al. Body mass index and survival in women with breast cancer- systematic literature review and meta-analysis of 82 follow-up studies. Ann Oncol. 2014; 25:1901–14.
3. Kroenke C, Chen W, Rosner B, Holmes M. Weight, weight gain, and survival after breast cancer diagnosis. J Clin Oncol. 2005; 23:1370–78.
4. Lynch B, Neilson H, Friedenreich C. Physical activity

and breast cancer prevention. Recent Results Cancer Res. 2011; 186:13–42.

5. Davis A, Kaklamani V. Metabolic syndrome and triple negative breast cancer: a new paradigm. Int J Breast Cancer. 2012; 2012:809291. doi:10.1155/2012/809291.

6. Berclaz G, Li S, Price KN, et al, for the International Breast Cancer Study Group. Body mass index as a prognostic feature in operable breast cancer: the International Breast Cancer Study Group experience. Ann Oncol. 2004; Jun; 15(6):875–84.

7. Park J, Morley T, Kim M, et al. Obesity and cancer—mechanisms underlying tumour progression and recurrence. Nat Rev Endocrinol. 2014; 10:455–465.

8. Campbell KL, Foster-Schubert KE, Alfano CM, et al. Reduced-calorie dietary weight loss, exercise, and sex hormones in post-menopausal women: randomized controlled trial. J Clin Oncol. 2012; 30:2314–26.

9. McTiernan A, Irwin M, VonGruenigen V. Weight, physical activity, diet, and prognosis in breast and gynecologic cancers. J Clin Oncol. 2010; 28:4074–80.

10. Buffart L, Galvao D, Brug J, et al. Evidence-based physical activity guidelines for cancer survivors: current guidelines, knowledge gaps and future research directions. Cancer Treatment Reviews. 2014; 40:327–40.

11. Dirat B, Bochet L, Dabek M, et al. Cancer-Associated Adipocytes exhibit an activated phenotype and contribute to breast cancer invasion. Cancer Res. 2011; 71:2455–65.

12. Ministry of Health, 2015b. New cancer registrations 2013, 2 December 2015, on line publication. Wellington: Ministry of Health, New Zealand.

13. WHO Consultation on Obesity. Obesity: preventing and managing the global epidemic: report of a WHO consultation (1999: Geneva, Switzerland). WHO Technical Report series, 894. ISBN 92 4 120894 5, ISSN 0512–3054.

14. Kawai M, Tomotaki A, Miyata H, et al. Body mass index and survival after diagnosis of invasive breast cancer: a study based on the Japanese National Clinical database – Breast cancer Registry. Cancer Medicine. 2016; 5:1328–40.

15. Matthews SB, Thompson HJ. The obesity-breast cancer conundrum: an analysis of the issues. Int J Mol Sci. 2016; 17:989; doi:10.3390/ijms17060989.

16. Yoo K, Tajima K, Park S, et al. Postmenopausal obesity as a breast cancer risk factor according to estrogen and progesterone receptor status(Japan). Cancer Letters. 2001; 167:57–63.

17. Suzuki R, Rylander-Rudqvist T, Ye W, et al. Body weight and post-menopausal breast cancer risk defined by estrogen and progesterone receptor status among Swedish women: A prospective cohort study. Int J Cancer. 2006; 119:1683–1689.

18. Ministry of Health, 2014. Selected Cancers 2011, 2012 & 2013, 17 September 2014, on line publication. Wellington: Ministry of Health, New Zealand.

19. Saadatmand S, Bretveld R, Siesling S, Tilanus-Linthorst M. Influence of tumour stage at breast cancer detection on survival in modern times: population based study in 173,797 patients. BMJ. 2015; Oct 6; 351:h4901. doi: 10.1136/bmj.h4901.

20. de Azambuja E, McCaskill-Stevens W, Francis P, et al. The effect of body mass index on overall and disease-free survival in node-positive breast cancer patients treated with docetaxel and doxorubicin-containing adjuvant chemotherapy: the experience of the BIG 02-98 trial. Breast Cancer Res Treat. 2010 Jan; 119(1):145–53. doi: 10.1007/s10549-009-0512-0.

21. Widschwendter P, Friedl T, Schwentner L, et al. The influence of obesity on survival in early, high-risk breast cancer: results from the randomised SUCCESS A trial. Breast Cancer Res. 2015; 17: 129. doi: 10.1186/s13058-015-0639-3.

22. Sparano J, Zhao F, Martino S, et al. Long-term follow-up of the E1199 Phase III Trial evaluating the role of taxane and schedule in operable breast cancer. J Clin Oncol. 2015 Jul 20; 33(21):2353–60.

23. Fontanella C, Lederer B, Gade S, et al. Impact of body mass index on neoadjuvant treatment outcome: a pooled analysis of eight prospective neoadjuvant breast cancer trials. Breast Cancer Res Treat. 2015 Feb; 150(1):127–39.

24. Pan H, Gray R, and Early Breast Cancer Trialists' Collaborative Group. Effect of obesity in premenopausal ER+ early breast cancer: EBCTCG data on 80,000 patients in 70 trials. J Clin Oncol, 2014 ASCO Annual Meeting Abstracts, 32 (15 Suppl), 2014; 503.

25. Scholz C, Andergassen U, Hepp P, et al. Obesity as an independent risk factor for decreased survival in node-positive high-risk breast cancer. Breast Cancer Res Treat. 2015 Jun; 151(3):569–76.

26. Abraham JE, Hiller L, Dorling L, et al. A nested cohort study of 6,248 early breast cancer patients treated in neoadjuvant and adjuvant chemotherapy trials investigating the prognostic value of chemotherapy-related toxicities. BMC Med. 2015 Dec 29; 13:306. doi: 10.1186/s12916-015-0547-5.